Screening for colorectal cancer

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SUMMARY

Colorectal carcinoma represents a major cause of cancer deaths in the United Kingdom. Tumours detected at an early or even premalignant stage have a better prognosis. In this review we consider the argument for screening for colorectal carcinomas and discuss the means available and the implications of implementing screening programmes using some of these methods. A suggestion is made for the more rational use of limited resources to target those at greatest risk.

INTRODUCTION

It is a humbling fact that, despite advances in medical knowledge and improved anaesthetic and surgical techniques, mortality rates for patients diagnosed as having colorectal cancer have changed little in the past three decades.[1] This reflects the advanced stage at time of diagnosis in many cases. It is accepted that the prognosis is dependent on the age of the patient, the differentiation of the tumour and the depth of invasion at the time of diagnosis.[2] Tumours which are restricted to the bowel wall (Dukes' A) are associated with a five year survival of 80%. These however account for less than 10% of colorectal lesions.[3,4] The low occurrence of early tumours represents a failure to prevent colorectal carcinomas. Prevention may be primary, where aetiological factors are recognised and avoided, or secondary, where the disease is detected sooner through screenings.[5]

There is now evidence that animal fats have a role in the aetiology of colorectal carcinoma, while a high intake of vegetable fibre is believed to protect against tumour development.[6,7] To implement primary prevention would require re-education of the population, with major changes in dietary habits and benefits would not become apparent for many years.

Before screening can be considered as a means of secondary prevention the disease must fulfil certain criteria:

a) the disease must have serious consequences in the population

b) an acceptable treatment must be available

c) prognosis must be improved by early detection

d) the incidence of the disease must be high enough to justify the cost of screening

e) an acceptable screening test must be available; this should be cheap, reliable, have a high degree of sensitivity and specificity and be acceptable to the population being screened.[5,8]

Colorectal cancer fulfils many of these criteria. It is the second leading cause of cancer deaths in the United States of America and Great Britain. Over 20,000 new cases were diagnosed in England and Wales in 1983, and 1,138 cases were diagnosed in Northern Ireland during 1991-92 giving an incidence of 35.8/100,000 of the population.[9,10,11]

As has been mentioned earlier, prognosis is improved if tumours are detected when restricted to the mucosa. It is now accepted that most carcinomas develop from adenomatous polyps as suggested by Morson and colleagues.[12] In theory colorectal cancer could be prevented by the

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detection of adenomatous polyps in the premalignant phase. Many of these are amenable to endoscopic removal, increasing the acceptability of the treatment available.

At present the criterion which colorectal cancer fails to fulfil is the availability of an acceptable screening test. The methods available to the clinician include:

- i) questionnaire
- ii) digital examination
- iii) rigid sigmoidoscopy
- iv) flexible sigmoidoscopy
- v) double contrast barium enema (DCBE)
- vi) colonscopy
- vii) faecal occult blood testing (FOBT)

Each of these has varying sensitivity and specificity and, as the investigations become more invasive, increasing morbidity and mortality.

QUESTIONNAIRE

Several studies have been undertaken to investigate the efficiency of a questionnaire in detecting colorectal neoplasia.[13, 14, 15] In using questionnaires it is possible to detect only those patients who are symptomatic and here one must assume that lesions will cause symptoms at an early premalignant stage of the disease. This is not supported by the presentation of colorectal neoplasia with up to 25% of those with colorectal carcinoma having disseminated disease at the time of diagnosis.[16, 17] In addition the high incidence of colonic symptoms in normal individuals or individuals with benign disease makes the specificity of questionnaires unacceptably low.[13, 14]

DIGITAL EXAMINATION

Digital examination while being cheap and easily performed fails both in acceptability and sensitivity, with approximately 10% of colonic neoplasia occurring within 10 cm of the anal margin.[18, 19]

RIGID SIGMOIDOSCOPY

Theoretically up to 25-40% of colorectal tumours should be visible with a rigid sigmoidoscope (i.e. up to 25 cms).[21, 22] In practice the instrument is rarely inserted to 25 cms and the view is often obscured by faeces.[19, 23] Screening programmes using rigid sigmoidoscopy have detected tumours in less than 0.2% of those screened.[24] The University of Minnesota Cancer Detection Center

has shown the benefits of rigid proctosigmoidoscopy claiming an 85% reduction in the statistically anticipated adenocarcinomas in those undergoing the examination routinely.[25] However the costs of such a screening programme are prohibitive with figures from the United States suggesting that only one tumour is detected per $70,000 expended.[2]

FLEXIBLE SIGMOIDOSCOPY

Flexible sigmoidoscopy has many advantages over rigid sigmoidoscopy. Up to 60 cms of rectum and colon can be examined, with 50-70% of polyps said to occur within this length of colon.[20] The examination is said to cause less discomfort than rigid sigmoidoscopy and can be performed with a minimum of bowel preparation. Interestingly two studies have shown no difference in detection of polyps when using a 35 cms scope compared with the 60 cms instrument.[27, 28] In spite of these advantages compliance has been poor in screening programmes using the flexible scope.[31] The positive predictive value is low; between 2-6% of asymptomatic patients screened were found to have adenomas >1 cm in diameter.[29, 30]

The disadvantages of flexible sigmoidoscopy are the need for training of the endoscopist, the capital outlay in providing the service and the time required. It must also be noted when using both flexible and rigid sigmoidoscopy that in recent years several reports have documented an increased incidence of right sided colonic tumours. This so called "shift to the right" will reduce the number of tumours within reach of the sigmoidoscope and may reduce the efficacy of this as a method of screening.[32, 33]

COLONOSCOPY

Colonoscopy provides the best opportunity for evaluating the colonic mucosa, with sensitivities and specificities of over 95% being achieved. It may also be a therapeutic procedure enabling pedunculated polyps to be removed. Its use as a population screening test is prohibited by time, expense and expertise required to perform the examination, with even an experienced endoscopist failing to reach the caecum in as many as 20% of examinations. Being more invasive it is associated with a higher complication rate with the risk of perforation reported as 1 in 500- 1 in 10,000.[24, 34, 36] Perforation is associated with a mortality of 5-10%.[36] It cannot be recommended for screening on a population basis

but should be the method of choice in the high risk groups.

BARIUM ENEMA

Barium enema has the advantage of permitting visualisation of the colon and rectum at a lower cost and with lower morbidity and mortality than colonoscopy. Criticisms of this as a population screening method include the cost, the lack of any therapeutic potential and the lower sensitivities and specificities when compared to colonoscopy. Double contrast barium enema can detect up to 90% of cancers or polyps over 1 cm in diameter.[35] Single contrast enema should be condemned as a screening test achieving sensitivities of only 0.41 for polyps and 0.7 for cancers.[37]

It must also be considered in the cost of the examination that should it prove positive then endoscopy may be required if polypectomy is considered. Barium enema alone is also an inadequate examination of the colorectum and should be combined with at least rigid sigmoidoscopy to improve visualisation of the rectosigmoid junction.

FAECAL OCCULT BLOOD TESTING

FOBT is often used as a preliminary diagnostic test in those presenting with non-specific abdominal symptoms. It is also used in elderly patients in whom it is considered advisable to avoid more invasive tests if possible.

The basis of the test is not the detection of blood in the stool but rather the detection of an elevated faecal blood level. It has been calculated that the median daily blood loss into the gut for normal subjects is 0.6-1.2 ml/day which is equivalent to a faecal haemoglobin concentration of <2 mg/g of faeces[20, 38, 39]

Bleeding from colorectal cancers has been shown to range from 0 to 75 ml/day with a median loss of 1.2 ml/day being recorded.[38, 39, 40]

The basis of most chemical tests is the oxidation of phenolic compounds by the addition of hydrogen peroxide. This is catalysed by haematin, a breakdown of haemoglobin in the gastro-intestinal tract. Compounds such as benzidine, orthotolidine or most commonly guaiac react with hydrogen peroxidase to give a colour change. To avoid false positives from substances similar to haematin (e.g. animal haemoglobin) it is recommended that a meat free, high fibre diet is taken for three days prior to testing. Other foods such as turnips, horseradish, salmon and sardines are also to be avoided.

The test is repeated over three consecutive days to account for variable blood loss. Stoehlein and colleagues report that a blood loss of greater than 10 ml per day will result in a positive FOBT in 90% of cases, while Hardcastle suggested a loss of 20 ml per day will result in a positive result in 89-90% of cases[20, 41] The sensitivity of the test can be further increased by prolonging the duration of the test from 3-6 days and by rehydrating the slides of faeces before testing.[42, 43, 44] However the decrease in false negative rate results in an increase in false positive rate, and with this a fall in the positive predictive value.

There are however problems with the test, in that in order for the reaction to occur degradation of haemoglobin is required. If, in the case of left sided lesions the blood has not been degraded then the test may negative, while in caecal lesions excessive degradation may occur, destroying the haematin required to catalyse the reaction, thus resulting in a negative FOBT. It is recognised for these reasons that caecal and rectal tumours may not be detected by FOBT.[45, 46] Attempts to eliminate the effects of diet have been made with the Haemoquant test designed to detect the conversion of haem to fluorescent porphyrins thus eliminating the effects of dietary peroxidases. It has the added advantage of being a quantitative test, permitting an estimation of the origin of the blood loss to be made since the total amount of haemoglobin and degraded haemoglobin can be measured.[47]

Immunological tests detecting human haemoglobin only have been developed. These are extremely sensitive, detecting haemoglobin in a concentration of 0.3 mg/g of faeces.[48] Such tests have increased detection of blood in the stool by up to 25% in comparison with the Haemoccult test. These tests are however more expensive and difficult to perform.[50, 51, 52] A combination test with the immunological component being performed only if the chemical test proves positive has been suggested.[49]

To determine if FOBT is of benefit five major controlled trials have been undertaken.[53, 54, 55, 56, 57, 58, 59, 60] To eliminate problems with length bias (i.e. better differentiated tumours are present in the community longer and are therefore more likely to be detected by screening), lead time bias

TABLE I

Summary of five major trials of Faecal Occult Blood Test for screening for colorectal carcinoma.

Study	Size	Compliance	Positive Test	Positive Predictive Value	
Minnesota	46,000	80% 1st year 70% later	1.8-3.5%	Invasive Ca. Polyps	29% 8%
Memorial Sloan Kettering	>20,000	74%	2.4%		12% 38%
Danish Study	60,000 41%	67%	1.1%		17%
Swedish Study	27,700	66%	1.9-5.8%		
Nottingham Study	100,000	52%	2.3%		11% 23%

(i.e. prolongation of survival is attributed to earlier diagnosis with death occurring at the same time) and selection bias (i.e. well motivated, health conscious, individuals are more likely to participate in screening programmes) it is necessary to compare morbidity and mortality of a group offered the screening test with an age sex matched group who are not screened.

The results are summarised in Table I. At best compliance is of the order of 70% falling as low as 52% in the early stages of the Nottingham trial.[8] Results regarding survival advantage are becoming available. The percentage of Dukes' A tumours in the screened groups is higher than in the control groups and as one would anticipate a survival advantage is being demonstrated in the screen-detected groups with Dukes' A and B tumours.[61, 62]

This is not the only criterion on which the feasibility of performing screening will be assessed. The cost of implementing such a programme is a major factor. Offering the screening test to those aged 50-65 years and assuming a positive FOB rate of 2% would result in approximately 1,250 colonoscopy examinations per million of the population assuming the percentage of those aged 50-65 remains constant. The cost would then increase as positive examinations required further endoscopy.

Due to a lack of controlled trials it has been necessary to resort to an elaborate mathematical model. A number of screening strategies have been considered incorporating a combination of procedures e.g. FOBT and sigmoidoscopy, FOBT and DCBE and FOBT and colonoscopy. The decrease in probability of developing colorectal cancer, increase in life expectancy and cost have been calculated.[63, 64, 65] The authors stress that each strategy must be compared in terms of efficiency, cost and inconvenience. The results suggest that annual FOBT might reduce mortality by 30% while annual colonoscopy could reduce mortality by 85%.[66] It is also suggested that annual FOBT combined with either 5 yearly DCBE or colonoscopy preserves 70-90% of the effectiveness of annual colonoscopic examination while reducing costs by 80%.[66]

The dilemma with which we are faced is that while preliminary results from controlled trials and mathematical models suggest that screening may be effective the cost of performing such a screening programme would be enormous. The numbers requiring endoscopy/DCBE following positive FOBT would necessitate a major expansion in the existing services.

A more rational use of limited resources would be the targeting of those at greatest risk. This would include those with a genetic predisposition

to cancer, and those with a long standing history of colitis.

Familial adenomatous polyposis which encompasses the diseases familial polyposis coli and Gardner's syndrome is an autosomal dominant condition characterised by the development of more than 100 adenomatous polyps in the colon and rectum. If not treated appropriately malignant change inevitably develops in one or more of these polyps. The genetic defect has been localised to chromosome 5. This has permitted genetic screening of those at risk, initially by linkage analysis but more recently by direct sequencing of the gene and mutation analysis. Northern Ireland has a high prevalence of familial adenomatous polyposis with an estimated 93 from 26 families having a 1 in 2 risk of having inherited the gene with a further 49 with a risk of 1 in 4.[67] Prior to DNA analysis, screening of those at risk was performed by regular sigmoidoscopic examination of the rectum. Such is the accuracy of DNA analysis that many of those at risk can either be eliminated or have the frequency of the endoscopic examinations greatly reduced. Colonoscopy can be reserved for those at greatest risk to monitor the colon and determine the optimum time for surgical intervention.

In contrast to FAP, hereditary non-polyposis colorectal cancer (HNPCC) lacks a readily identifiable premalignant marker of the disease. The diagnosis is dependent on an accurate family history which often is not available. The penetrance of the gene is 70-80%. These factors may make it difficult to label a family as an HNPCC kindred with confidence. HNPCC families are said to account for 2-5% of all colorectal tumours, although published data would suggest that in Northern Ireland the incidence is at the lower end of the spectrum.[68] To date 4 genes have been implicated in HNPCC, thus making DNA analysis more difficult.[68] Unlike FAP in which DNA analysis is well established the mainstay of screening HNPCC families remains identification of families at risk followed by regular visualisation of the colon. It is recommended that HNPCC kindred members undergo 3-yearly colonoscopy beginning at 25 years of age although some would suggest that this should be increased to annual examination after 35 years of age.[69, 70]

There are also a number of families who while failing to fulfil the strict criteria for an HNPCC

kindred undoubtedly have an increased risk (see Tables II and III). We would recommend that patients in whom the life time risk is increased to greater than 1 in 10 be included in the screening programme.

The final group with an increased risk of developing colorectal carcinoma are those with a longstanding history of colitis. The association between ulcerative colitis and carcinoma is well established in those with a pancolitis, poor control, and disease ongoing for greater than 10 years. Gyde and colleagues reported an 8-fold increase

TABLE II

Amsterdam criteria for diagnosis of Hereditary Non-polyposis Colorectal Cancer (HNPCC) kindreds

i)	Three or more relatives with histologically verified colorectal cancer, one of them being a first degree relative of the other two.
ii)	At least two consecutive generations should be affected.
iii)	In one of the relatives colorectal cancer should be diagnosed at under 50 years of age.

(Vassen H F, Mecklin J-P, Meera Khan P, Lynch H T. The international collaborative group on hereditary non-polyposis colorectal cancer (ICG-HNPCC) Dis Colon Rectum 1991; 34: 424-5)

TABLE III

Cancer risk in first degree relatives of patients with colorectal carcinoma

Population risk	1 in 50
One relative affected (any age)	1 in 17
One first degree & one second degree	1 in 12
One relative under 45 affected	1 in 10
Two first degree relatives affected	1 in 6
Dominant pedigree	1 in 2

in risk of developing colorectal cancer in a group of over 200 patients with ulcerative colitis when compared with the general public. Within this group those with extensive colitis had a 19-fold increase in risk of developing malignancy.[71]

We believe screening of these high-risk groups represents the best use of limited resources. Implementation of a population screening programme using FOBT would require an enormous expansion of endoscopy services for a very low yield in terms of significant pathology detected per thousand patients screened. Colonoscopy of high-risk groups would require minimal expansion of existing endoscopy services and has the potential for identifying up to 10% of colorectal carcinomata at an early stage, or indeed preventing their development by detection of premalignant adenomas.

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